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10/562,377	08/25/2006	Cathy Lofton-Day	47675-163	3075

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,377	LOFTON-DAY ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-14,16,18,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-14,16,18,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/01/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 1-10, 12-14, 16, 18, 23-24 in the reply filed on 6/08/2009 is acknowledged.

Based upon amendments to the claims, the requirement for the specific election of a combination of SEQ ID numbers is withdrawn. As such the arguments towards the requirement for election are moot. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement between Group I and II, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-10, 12-14, 16, 18, 23-24 are pending. Claims 11, 15, 17, 19-22, and 25 have been cancelled.

3. An action on the merits for claims 1-10, 12-14, 16, 18, 23-24 is set forth below.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 4/01/2008 has been considered by the examiner.

Drawings

5. The drawings submitted on 12/23/2005 have been accepted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-10, 12-14, 16, 18, 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10, 12-14, 16, 18, 23-24 are indefinite because the claims do not recite a clear nexus between the preamble of the claim and the process steps of the claims. The preamble states a method for detecting or detecting and distinguishing between or among colorectal cell proliferative disorders. The positive active steps of the claims are drawn to contacting genomic DNA with at least one reagent that distinguishes between methylated and nonmethylated CpG dinucleotides. The claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are steps of detecting or detecting and distinguishing between or among colorectal cell proliferative disorders. Because these steps are missing there is no positive active step to detecting or detecting or distinguishing between or among colorectal cell proliferative disorders.

Claims 4 and 6 are indefinite over the phrase “detecting and distinguishing between or among colorectal cell proliferative disorders is, at least in part, enabled” (last two sentences of claim 4 and claim 6). This phrase is indefinite because it is not clear the metes and bounds of “at least in part, enabled”. It is not clear how the "at least in

part, enabled" limits the claim and as such it is not clear which parts of the detection are enabled.

Claim Rejections - 35 USC § 112/Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-10, 12-14, 16, 18, 23-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

The claims are draw to a method of detecting or detecting and distinguishing between or among colorectal cell proliferative disorders comprising a step to distinguish

between methylated and non-methylated CPG dinucleotides within a target sequence of a genomic DNA comprising SEQ ID No. 6 or 21.

The claims therefore are broadly drawn to detecting any colorectal cell proliferative disorder and distinguishing among colorectal cell proliferative disorders in any subject by detection of any different in methylated and non-methylated CpG dinucleotides in the sequence of SEQ ID NO. 6 and 21. When the claims are read in light of the specification, the specification does not provide predictable guidance and the art, as presented below, that such correlations are unpredictable.

Nature of the Invention

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

The specification asserts that characteristics of methylation and nonmethylated CPG dinucleotides are associated for detecting or detecting and distinguishing between or among colorectal cell proliferative disorders such as colorectal carcinoma, colon adenomas, and colon polyps (p. 5 lines 15-25). The specification asserts that the invention provides a method of determining based on at least distinguishing the methylation state of at least one target CpG dinucleotides sequences or an average methylation state of a plurality of target CpG dinucleotides sequences colon cell proliferative disorders (p. 6 lines 5-20). However, the instant specification has not

provided any guidance as to which CpG dinucleotides are associated with colorectal cell proliferation. The instant specification has not provided any guidance as to which methylation states must be detected to be associated with each particular colorectal cell proliferative disorder. The instant specification has not provided any guidance as to which differences in methylation are associated with differentiating between the different types of colorectal cell proliferative disorders.

The specification provides figures; however, none of these figures are drawn to CpG sites within SEQ ID No. 6 or 21. Specifically these figures disclose CpG sites in SEQ ID NOs. 1-3. Therefore the drawings in the instant application do not provide guidance to the detection of colorectal cell proliferative disorder by determining the methylation status of SEQ ID No. 6 or 21.

The instant specification does not provide a definition for the term "subject". As such "subject" can be considered any species including dog, cat, and human. The instant specification has not provided guidance to determine if a correlation of methylation status in one species can be extrapolated to any other species. Further the art teaches that such methylation status is species dependent.

The instant specification discloses various methodologies to detect CpG methylation status (p. 12-13 and p. 15-17). However, the specification does not disclose the determination of colorectal cell disorder by detection of CpG methylation status in SEQ ID No. 6 or 21 in any of these various methodologies.

The specification asserts that the present invention provides the use of a bisulfite technique for determination of the methylation status of CpG dinucleotides sequences

within genomic sequences of SEQ ID No. 6 and 21 and that such determination has diagnostic and prognostic utility (p. 13 lines 15-20). However, the specification has not provided any guidance or data for the association of the methylation status of CpG dinucleotides sequences within genomic sequences of SEQ ID NO. 6 and 21 and colorectal proliferative disease. The art, as described below, teaches that such associations are unpredictable and do no make for good cancer diagnostic markers.

The specification asserts that the instant invention is based upon the analysis of methylation levels within SEQ ID No. 6 or 21 (p. 17 lines 24-25). The specification asserts that particular embodiments provide an application of the analysis of methylation levels and/or patterns within said sequences that enables a precise detection, characterization and/or treatment of colon cell proliferative disorders (p. 17 lines 26-30). However, the specification has not provided any guidance or data for the association of the methylation status of CpG dinucleotides sequences within genomic sequences of SEQ ID NO. 6 and 21 and colorectal proliferative disease.

The specification asserts that the instant invention enables diagnosis and/or prognosis of cancer base upon a measurement of differential methylation of one or more CpG sequences of SEQ ID NO. 6 and 21 (p. 30 lines 28-p. 31 lines 1-5). However, the specification has not provided any guidance or data for the association of the methylation status of CpG dinucleotides sequences within genomic sequences of SEQ ID NO. 6 and 21 and colorectal proliferative disease. The art, as described below, teaches that methylation markers do not make for predictable markers for clinical diagnosis of cancer.

The specification provides examples. Example 1 is based upon pooled genomic DNA from healthy colon, adenomas, and colon adenocarcinoma tissue (p. 32 lines 1-5). The instant specification provides method steps to AP-PCR (p. 37-38). The specification presents Table 4 which is a selection of the results of AP-PCR and disclosure of the methylation state of tissue types. It is noted that none of these primers have been associated with the SEQ ID numbers which are claimed in the claim set. The rest of example 1 on p. 40-42 discloses scoring of methylation patterns; however, this example does not disclose any working example of detection of methylation patterns in SEQ ID NO. 6 or 21.

Example 2 is drawn to differentially methylated fragments are compared to the human genome using the BLAST utility in the Ensembl database (p. 32 lines 8-10). The instant specification provides the methodology for bisulfite sequence (p. 43-45. However does not provide any data for SEQ ID No. 6 or 21.

In summary, the claims are drawn to detection of any colorectal cell proliferative disorder or distinguishing between any colorectal cell proliferative disorders in any subject, however, the specification does not provide a predictable correlation of any methylation status of SEQ ID NO. 6 or 21 to such a correlation.

The predictability or unpredictability of the art and degree of experimentation

The art does not disclose that SEQ ID 6 or 21 are fragments of any known gene associated with colorectal cell proliferative disorder.

Ehrlich et al. (2002 Oncogene Vol 21 p. 5400) teaches that hypomethylation and

hypermethylation of DNA are relative terms and demote less or more methylation than in some standard DNA (p. 5400 last paragraph). Ehrlich et al. teaches that there are considerable differences in the amounts and distribution of DNA methylation among different vertebrate tissues because DNA methylation is not only species-specific but also tissue-specific (p. 5400 last paragraph). Therefore the association in one species of CpG islands to cancer type cannot be extrapolated to any species predictably. Because the distribution of DNA methylation varies between species it is not predictable that the same methylation status differences observed in one species is correlative in another species.

The art teaches that there is an unpredictability based on reference comparison and sample type.

Ehrlich et al. teaches that therefore unless the studied tumor DNA is being compared to a relatively pure population of cells which is know to be the cell of origin of the tumor it is best to use DNA from a variety of normal tissues as the control (p. 5401 1st column 1st paragraph). Ehrlich et al. teaches that also in identifying cancer-specific differences in genome methylation that the studied cells should be uncultured cell populations because of the frequent changes in DNA methylation that occur upon cell culture (p. 5401 1st paragraph). Therefore Ehrlich et al. teaches that not all cell populations (e.g. samples) have the same correlation to methylation.

Ehrlich et al. teaches that how early DNA hypomethylation can be detected during tumorigenesis may depend on the type of tumor as well as the individual tumor sample (p. 5401 2nd column 1st paragraph). Therefore the art teaches that there is

unpredictability in diagnosing cancer in any sample type and such correlations are sample specific.

The art teaches that the correlation of methylation statues to cancer is unpredictable. Ehrlich et al. teaches that a correlation to cancer would not have been found in only one CpG island and one normal tissue type was used.

Ehrlich et al. teaches that hypermethylation of 12 CpG islands at the 5' end of tumor suppressor genes was investigated in a methylation sensitive PCR of 600 cancers (p. 5403 1st paragraph). Ehrlich et al. teaches that cancer-associated hypermethylation was found in most tumors of a given type in at least a few of the CpG islands however the pattern of which CpG islands are hypermethylation varied with the kind of cancer (p 5403 1st paragraph). Ehrlich et al. teaches that this hypomethylation probably would have been missed if the analysis for methylation had not been quantitative and had not included a variety of normal tissue DNAs (p. 5408 1st full paragraph last sentence).

The art teaches that generally methylation is not used for diagnostic markers.

Cottrell (clinical Biochemistry 2004 Vol. 37 p. 595) teaches that because methylation-based markers are not routinely used in clinical labs, the methodology has not been fully optimized, validated, and standardized. Cottrell et al. teaches that most of the methylation methods rely on bisulfite treatment protocol which must meet strict requirements for consistency and performance (p. 601 1st column 2nd full paragraph). Cottrell et al. teaches that in order to discover optimal markers and crease successful assays, there will need to be clearly defined clinical questions, sample sets, and

methodologies coupled with the current methylation technologies (p. 601 1st column last paragraph).

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance as to how to correlate detection of any colorectal proliferative disorder or distinguishing between any colorectal cell proliferative disorders to methylation status of SEQ ID NO. 6 or 21 in any animal. The specification does not provide any data to the association of methylation status of SEQ ID NO. 6 or 21 in any subject to colorectal proliferative disorder. The specification does not provide any data to distinguish between colorectal cell proliferative disorders using the methylation status of SEQ ID No. 6 or 21. Neither the specification nor the art discloses that SEQ ID No. 6 or 21 are associated with a gene associated to colorectal cell proliferative disorders. The art teaches that methylation markers are not used as diagnostic markers because of the unpredictability in determining methylation status. The art teaches that methylation is species and tissue dependent. The art teaches that such correlations can not be extrapolated between cancer types. The art teaches that multiple reference samples must be used and multiple CpG islands.

The skilled artisan, therefore, would have to perform undue experimentation to determine the correlation of colorectal cell proliferative disorder in any subject based on methylation status of SEQ ID NO. 6 or 21.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written. The skilled artisan would have to determine which CpG islands in SEQ ID NO. 6 or 21 were correlative to colorectal cell

proliferative disorders. The skilled artisan would have to test methylation status in many species without an expectation of a predictable success in of detection in each species type. The skilled artisan would have to test multiple sample types and CpG islands in multiple types of colorectal cell proliferative disorders. The skilled artisan would have to detect multiple reference samples.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide a predictable correlation of any CpG methylation status change in SEQ ID NO. 6 or 21 in any subject to detect colorectal cell proliferative disorder or to distinguish between colorectal cell proliferative disorders. Further, the art teaches that this correlation would be different depending on the number of CpG islands tested and the reference samples which were compared. Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday-Friday 8AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Sarae Bausch/
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